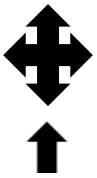
eCB signaling-microbiota partnership in ASD	bjects /System model	Major Effects		Study
Gut microbiota dysbiosis *Lactobacillus acidophilus* supplementation	Human HT-29 epithelial cells	Dysregulates the intestinal eCB system Increased intestinal cells CB2 receptor mRNA expression		**Rousseaux et al., 2007**
eCB and PEA faecal levels	General population	Prediction of the association between gut microbial diversity and anhedonia		**Minichino et al., 2021**
Prebiotic treatment: mucin-degrading Gram-negative bacterium	Children with ASD	A. muciniphila supplementation improves gut permeability/ increases 2-AG intestine levels		**Everard et al., 2013**
Prebiotic treatment: mucin-degrading Gram-negative bacterium	Children with ASD	*A. muciniphila* supplementation provides beneficial effects dependent on eCB-derived lipids of the 2-AcGs family		**Depommier et al., 2021**
Mucin-degrading Gram-negative bacterium	Children with ASD	Decreased *A. muciniphila* abundance		**Wang et al., 2011**
Mucin-degrading Gram-negative bacterium	Children with ASD	Increased A. muciniphila abundance		**De Angelis et al., 2013**

Ultramicronized PEA + Luteolin coadministration	ASD-like BTBR mouse model	Decreased ASD-like repetitive behavior/ pro-inflammatory cytokine production/ intestinal permeability/ Increased sociability	⬇ ⬆	**Cristiano et al., 2018**
B. longum probiotic mix (including *Lactobacillus acidophilus and B. infantis*) supplementation	*zebrafish*	Increase intestinal mRNA expression of Cnr1 and Cnr2 genes Decrease of *faah* and mgll gene expression	⬆ ⬇	**Gioacchini et al., 2017**
B. fragilis supplementation	ASD-like MIA model	Improves social-communicative deficits/ integrity intestinal barrier	⬆	**Hsiao et al., 2013**
Bifidobacterium longum	Children with ASD	ASD depletion of *B. longum* Decrease butyrate-producing bacteria	⬇	**Coretti et al., 2018** **Sugahara et al., 2015**
Butyrate treatment	ASD-like VPA and BTBR models	Improvement memory and social behavior	⬆	**Takuma et al., 2014** **Kratsman et al., 2016**
Butyrate and butyrate-producing bacteria	Children with ASD	Lower levels of butyrate and abundance of *Lachnospiraceae*	⬇	**Liu et al., 2013**

Butyrate treatment (concentration-dependent effects)	Epithelial cell line Caco-2	Decrease eCBs synthetizing enzymes (i.e., NAPE-PLD; DAGL)		**Hwang et al., 2021**
eCB system and signaling	Children with ASD vs ASD-like VPA murine model	eCB signaling FAAH and MAGL increased expression Decrease of 2-AG serum levels	  	**Zou et al., 2021**
Vitamin D	Vitamin D deficiency pregnancy Vitamin D supplementation	Risk of ASD Improve expression ASD symptoms	 	**Lee et al., 2021** **Principi and Esposito, 2020**
PEA and vitamin D	Epithelial cell line Caco-2	CB2 receptor activation		**Morsanuto et al., 2020**
Microglial cells morphology	ASD subjects	Changes in microglial cells phenotype (e.g., decreased ramified microglia)		**Lee et al., 2017**
PEA availability	Primary microglia cell culture	Increase microglial phagocytic/ Migratory activity		**Guida et al., 2017**
CBDV supplementation	ASD-like VPA murine model	Microglia activation/ Decrease deficit social behavior/ Upregulation CB2 RS	  	**Zamberletti et al., 2019**
Bacteroides	ASD subjects	Reduced levels		**Cao et al., 2021**

Bacteroides	eCB-like production	High affinity GPR119 (2-OG and OEA)	↑	**Cohen et al., 2017**
Systemic inflammation	ASD-like MIA murine mice	Segmented filamentous bacteria (SFB) promotes TH17 intestinal biogenesis	↑	**Farkas et al. 2015** **Kim et al., 2017**
	Mice lacking SFB	TH17-induced increase IL17-a plasma levels	↑	
		Failure of MIA-induced ASD-like symptoms	↓	
AEA, Δ9-THC, CBD administration	TH17-driven diseases	Microglia activation/	↑	**Kozela et al., 2019;** **Jackson et al., 2014**
		Decrease deficits social behavior/	↓	
		Upregulation CB2 Rs	↑	
Lactobacillus plantarum supplementation	Cecum and colon samples	Decrease SFB abundance	↓	**Fuentes et al., 2008**
SCFAs supplementation Physical exercise	Gut microbiota-eCB system interaction	Anti-inflammatory activity via eCB signaling Increase SCFA-dependent AEA, OEA and PEA levels AEA and OEA correlation with SCFAs receptor expression	↑	**Vijay et al., 2021**

TABLE 2
Summary table of the key studies involving eCB signaling and gut microbiota crosstalk in both patients with ASD and ASD-like animal models.